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jc813 U.S. PTO 11/21/00

PTO/SB/05 (08-00)
Approved for use through 10/31/2002. OMB 0651-0032
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	
First Inventor	Dean, Herbert et al.
Title	Cardioprotective Dosage Units
Express Mail Label No.	EK814081417

jc918 U.S. PTO 09/717746 11/21/00

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. [✔] Applicant claims small entity status. See 37 CFR 1.27.
3. [✔] Specification [*Total Pages* 11] *(preferred arrangement set forth below)*
   - Descriptive title of the invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. [ ] Drawing(s) *(35 U.S.C. 113)* [*Total Sheets*]
5. Oath or Declaration [*Total Pages* 2]
   a. [✔] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63 (d)) *(for continuation/divisional with Box 17 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
6. [ ] Application Data Sheet. See 37 CFR 1.76
7. [ ] CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

ACCOMPANYING APPLICATION PARTS

9. [ ] Assignment Papers (cover sheet & document(s))
10. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
11. [ ] English Translation Document *(if applicable)*
12. [✔] Information Disclosure Statement (IDS)/PTO-1449 [✔] Copies of IDS Citations
13. [ ] Preliminary Amendment
14. [✔] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [ ] Other: .....

17. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. _____/_____

Prior application information. *Examiner* _____ *Group / Art Unit* _____

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

18. CORRESPONDENCE ADDRESS

[✔] *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* or [ ] *Correspondence address below*

23580

Name	PATENT TRADEMARK OFFICE				
Address					
City		*State*		*Zip Code*	
Country		*Telephone*		*Fax*	

Name (Print/Type)	Robert R. Deleault, Esq.	*Registration No. (Attorney/Agent)*	39,165
Signature		*Date*	11/21/00

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FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT ($) 355.00

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Dean, Herbert et al.
Examiner Name	
Group Art Unit	
Attorney Docket No.	

METHOD OF PAYMENT

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:
   Deposit Account Number
   Deposit Account Name
   ☐ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17
   ☐ Applicant claims small entity status See 37 CFR 1.27
2. ☑ **Payment Enclosed:** ☑ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	$ 355
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 355.00

2. EXTRA CLAIM FEES

		Extra Claims		Fee from below	Fee Paid
Total Claims	13	-20** = 0	X	$ 9	= 0.00
Independent Claims	2	- 3** = 0	X	$ 40	= 0.00
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	80	209	40	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 355.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR § 1.129(b))	
179	710	279	355	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) $ 0.00

SUBMITTED BY

Complete *(if applicable)*

Name (Print/Type)	Robert R. Deleault, Esq.	Registration No. (Attorney/Agent)	39,165	Telephone	(603) 668-1971
Signature				Date	11/21/00

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Cardioprotective Dosage Units

This application claims the benefit of US Provisional Application No. 60/227,249, filed August 1, 2000.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to treatments for reducing the risk of cardiovascular disease. Particularly, the present invention relates to combinations of agents that antagonize beta-adrenergic function and agents that reduce platelet aggregation. More particularly, the present invention relates to beta-blocker agents and agents to reduce platelet aggregation for the treatment of cardiovascular disease and for the purpose of reducing medication error and increasing therapeutic compliance.

2. Description of the Prior Art

Cardiovascular disease is responsible for about 40% of the deaths in industrialized countries. Two categories of agents are commonly utilized to reduce morbidity and mortality from these diseases: agents that reduce platelet aggregation and agents that induce blockade of the adrenergic nervous system.

Platelet aggregation is an important factor in the pathogenesis of cardiovascular diseases. Antiplatelet agents have been shown to be effective in preventing cardiovascular disease. Aspirin is an example of such an agent. Two large primary prevention trials of aspirin have been completed in healthy men. The largest of these, the Physicians' Health Study, enrolled 22,071 apparently healthy male physicians aged 40 to 84. A 44% reduction in nonfatal heart attacks was observed in those taking 325 mg of aspirin every other day. In a similar trial in Britain, an overall 32% reduction in the risk of first non-fatal heart attack appears to

be associated with aspirin prophylaxis. The U.S. Preventive Services Task Force recommends aspirin for the primary prevention of myocardial infarction in men 40 years old and older in whom risk of myocardial infarction is sufficiently high to warrant risking the possible adverse effects of the drug. Meta-analysis of randomized secondary trials involving people with a history of occlusive vascular disease have demonstrated that aspirin reduces the subsequent incidence of heart attack, stroke and death by about 25% in both men and women.

Despite this compelling clinical evidence, many individuals at risk fail to benefit from such treatment. One perception underlying this failure is that the importance of aspirin in preventing cardiovascular disease may be trivialized by lay individuals because of its familiarity, its availability and its use is, therefore, dismissed. Some individuals instructed to take both a prescription medication and aspirin may assume that the prescription is more potent. Consequently, they fail to adhere to taking aspirin. Some individuals may not elect to pay for an over-the-counter product, desiring rather, to obtain a prescription that would be reimbursed by insurance.

Another category of agent commonly utilized, as a preventative measure in treating cardiovascular disease are the beta-adrenergic blocking agents. Examples of such agents listed in the current Physicians Desk Reference (PDR 2000) include propanolol, atenolol, timolol maleate, carteolol, penbutolol, nadolol, acebutolol hydrochloride, and metaprolol succinate. Indications for these agents include treatments for hypertension, angina pectoris due to coronary atherosclerosis, cardiac arrythmias, and reduction of cardiovascular mortality in patients who have survived the acute phase of myocardial infarction.

More than 500,000 Americans die from heart disease each year, the leading cause of death in the U.S. The American Heart Association estimates that the total annual cost of medical care and lost productivity due to heart disease is $12 billion to $24 billion. Annually, 1.5 million Americans suffer a heart attack, and people who have had a heart attack are at high risk of having another one. Large studies

indicate that tens of thousands of lives could be saved each year if more people were utilizing a beta-blocker after having a heart attack. One study done at the University of Maryland reviewed medical records of more than 200,000 people who had suffered a heart attack, 34% of whom received beta-blockers. During the next two years, people treated with beta-blockers had a 40% lower mortality rate compared to those who had not. Another notable report from Yale University disclosed that one year after a heart attack, patients over 65 years of age who had not taken beta blockers were 14% less likely to be alive than those who had taken them.

The concomitant use of aspirin is generally also indicated in the conditions previously described. It is particularly important in individuals suffering angina pectoris due to coronary atherosclerosis and in individuals who have survived the acute phase of myocardial infarction. Individuals with these disorders are known to commonly utilize many medications. Decreased compliance is known to occur when multiple medications are used.

The problems of achieving compliance with these cardioprotective agents include the inconvenience of taking multiple dosage units over a long period of time, the lack of immediately noticeable beneficial effects from such medications which might otherwise encourage use, trivialization of common medications such as aspirin, inconvenience of the requirement to obtain some medications by prescription and some over-the-counter, unwillingness to make out of pocket purchases, and confusion in older individuals, the age group in which these medications are typically required. Cost factors as well as outcomes must also be considered. Any improvements in compliance can save medical expenditures.

Simplification is a desired goal. Many of the above-mentioned problems can be ameliorated by incorporating the desired beta-adrenergic blocking agents and antagonists of platelet function into a single dosage unit. Successful prophylactic therapy is clearly preferable and less costly, compared to treatment for symptomatic

disease, prolonged illness, and/or disability, which require expensive medical resources including clinic visits, hospitalizations, and major cardiovascular surgery.

Therefore, what is needed is a device and method that combines agents that antagonize beta-adrenergic function and agents that reduce platelet aggregation. What is further needed is a device and method that includes the administration of a single dose.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a unitary oral cardiovascular protective medicinal formulation comprising a platelet aggregation inhibitor and a beta-adrenergic antagonist. It is another object of the present invention to provide a method for enhancing compliance with preventive measures for cardiovascular disease by providing an oral formulation comprising a platelet aggregation inhibitor and a beta-adrenergic antagonist, and administering the formulation to a patient in need thereof.

The clear need for cardiovascular preventive treatment, and the failure of patients to avail themselves of such treatment underscores the present need for the formulations of the present invention.

The present invention achieves these and other objectives by providing a system for the treatment of cardiovascular disease that requires a combined single dosage unit regimen and a method for reducing medication error and enhancing therapeutic compliance of combined medication agents for treatment of such disease. The system includes a single dosage unit that combines at least an agent for antagonizing beta-adrenergic function and an agent for reducing platelet aggregation, and preferably instructions for administering the single dosage unit. The single dosage unit may also contain one or more of folic acid, vitamin B6, vitamin B12, and vitamin E. The present invention also includes a method of reducing medication error and enhancing therapeutic compliance of combined agents for the treatment of cardiovascular disease. The method includes formulating

in a single dosage unit a beta-adrenergic blocking agent and a platelet inhibitor, and preferably instructing the use of the single dosage unit for treating cardiovascular disease. The method also includes formulating in a single dosage unit one or more of folic acid, vitamin B6, vitamin B12, and vitamin E.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The following detailed description of the invention is provided to aid those skilled in the art in practicing the present invention, however, it should not be construed to unduly limit the present invention. Variations and modifications in the disclosed embodiments may be made by those of ordinary skill in the art without departing from the scope of the present invention.

Compliance with medication is an important consideration in preventing or otherwise treating medical disorders. The simpler the medication regimen, the better the adherence over time. The present invention simplifies the dosing of a plurality of medications for both primary as well as secondary prevention of cardiovascular disease by a single dosage formulation. The present invention simplifies dosing of a plurality of medications for both primary as well as secondary prevention of cardiovascular disease preferably using a single dosage, once-a-day formulation. The present invention provides the components of a regimen for preventing cardiovascular disease in a convenient manner, compared to the current need to purchase individual components.

The present invention provides a single dosage unit that incorporates a beta-adrenergic antagonist and an agent to prevent platelet aggregation in accord with scientific evidence of their efficacy. Other agents may also be incorporated. Examples of other desirable components include the vitamins B6, B12 and folic acid, essential nutritional cofactors in the metabolism of homocysteine. Homocysteine elevation is an independent risk factor in vascular disease and a five-year prospective study has shown that the risk of heart attack for individuals with elevated homocysteine levels is 3.4 times greater in subjects with elevated homocysteine

levels. In individuals with elevated homocysteine, lowering of levels usually responds to supplementation with folic acid. In some instances supplementation with vitamins B6 and B12 may also be necessary to lower homocysteine levels.

The inclusion of folic acid in formulations of the present invention in the range of about 200 mcg to about 2000 mcg is considered desirable. It is also desirable to include folic acid, along with B6 in the range of about 2 mg to about 300 mg, or B12 in the range of about 10 mcg to about 1000 mcg, or both, so as to assure normal homocysteine levels.

The naturally occurring antioxidant, vitamin E is another example of an agent that is known to prevent coronary artery disease and strokes and which is considered desirable for inclusion in formulations of the present invention. Epidemiological data has shown a reduction of cardiovascular risk with vitamin E supplementation of at least 100 IU/day. This benefit does not occur at lesser dosages such as a 30 IU/ day replacement dosage typical of multivitamin use. In a study of 39,000 health professionals followed for four years, men with a median intake of 419 IU/day of vitamin E had a 44% relative risk reduction compared to men whose median intake was 6 IU/day.

The present invention anticipates that any or all of the active components of the dosage unit may be prepared for immediate release, or if desired, delayed release so as to alter rate of absorption. Materials and methods by which this may be accomplished are well known in the art, for example, by employing hydrophilic matrix materials such as methylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose.

The present invention further anticipates formulations that require dosing schedules of more than once a day, although once-a-day dosing is preferred. The present invention also anticipates that formulations may be in tablet, capsule, caplet, syrup, liquid, or other dosage forms commonly employed for oral administration of medicaments.

The following are examples of proposed formulations of the present invention containing both a beta-adrenergic antagonist and an antiplatelet agent.

Example 1

The synthetic beta1-selective adrenoreceptor blocking agent, atenolol, in a range from about 10 mg to about 100 mg combined with the antiplatelet agent, aspirin, in a range from about 30 mg to about 600 mg to form a single dosage unit. A preferred formulation is a single dosage unit of 25 mg of atenolol combined with 80 mg of aspirin, preferably taken once a day.

Example 2

The formulation of Example 1 which further includes folic acid in a range of about 200 mcg to about 2000 mcg, vitamin B12 in a range of about 10 mcg to about 1000 mcg, vitamin B 6 in a range of about 2 mg to about 300 mg, and vitamin E in a range of about 100 IU to about 800 IU.

Example 3

The synthetic adrenoreceptor antagonist propanalol hydrochloride in a range from about 10 mg to about 300 mg combined with the antiplatelet agent, aspirin, in a range from about 30 mg to about 600 mg to form a single dosage unit. A preferred formulation is a single dosage unit containing 60 mg of propanalol hydrochloride combined with 30 mg of aspirin. The formulation is to be taken three times a day.

Example 4

160 mg of propanalol hydrochloride in a sustained release formulation suitable for once-per-day dosing combined with 80 mg of aspirin. The formulation is to be taken once a day.

Example 5

10 mg of the non-selective beta-adrenoreceptor blocking agent timolol maleate combined with 30 mg of aspirin. This formulation might be taken twice a day for long-term prophylactic use in patients who have survived the acute phase of myocardial infarction.

Example 6

100 mg of the beta1-selective beta-adrenoreceptor blocking agent metoprolol tartrate combined with 80 mg of aspirin. This formulation might be taken twice a day for long-term prophylactic use in patients who have survived the acute phase of myocardial infarction.

These examples are not meant to be inclusive and it is contemplated that other dosages, other beta-blocking agents, and other platelet-active agents that exert preventative effects on cardiovascular disease by altering platelet adhesion, aggregation, and/or release of platelet factors, when incorporated together into a single formulation, are within the scope of this invention.

Various modifications and alterations of the present invention may be appreciated based on a review of this disclosure, and such changes and additions are intended to be within the scope and spirit of this invention as defined by the following claims.

What is claimed is:

1. A medicament dosage unit comprising a beta-adrenergic blocker and a platelet inhibitor.

2. The dosage unit of Claim 1 wherein said dosage unit is formulated as a once-a-day dosage unit.

3. The dosage unit of Claim 1 wherein said platelet inhibitor is aspirin.

4. The dosage unit of Claim 1 wherein said beta-adrenergic blocker is atenolol.

5. The dosage unit of Claim 1 wherein said beta-adrenergic blocker is propanolol.

6. The dosage unit of Claim 1 wherein said beta-adrenergic blocker is timolol.

7. The dosage unit of Claim 1 wherein said beta-adrenergic blocker is metaprolol.

8. The dosage unit of Claim 1 further comprising one or more of folic acid, vitamin B6 and vitamin B12.

9. A method of treating cardiovascular disease said method comprising formulating a single dosage unit comprising a beta-adrenergic blocking agent and a platelet inhibitor.

10. The method of Claim 9 further comprising indicating the use of said dosage unit for treating cardiovascular disease.

11. The method of Claim 9 further comprising providing instructions for administering said single dosage unit.

12. The method of Claim 9 wherein said formulating step further includes formulating said single dosage unit with one or more of folic acid, vitamin B6 and vitamin B12.

13. The method of Claim 9 wherein said formulating step further includes formulating said single dosage unit as a once-a-day dosage unit.

ABSTRACT

A single dosage medication formulation incorporating a beta-adrenergic antagonist and an agent to prevent platelet aggregation to enhance simplicity, convenience, and compliance with the use of these agents.

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

I, Herbert M. Dean, declare that I am a citizen of the United States of America, residing at and with a Post Office address of 30 Avalon Road, Waban, MA 02468, I, Robert E. Weinstein, declare that I am a citizen of the United States of America, residing at and with a Post Office address of 177 Commonwealth Avenue, Boston, MA 02116, and I, Allan M. Weinstein, declare that I am a citizen of the United States of America, residing at and with a Post Office address of 9205 Pegasus Court, Potomac, MD 20854, and that we verily believe that we are the original, first, and joint inventors of the **CARDIOPROTECTIVE DOSAGE UNITS** described and claimed in the attached Specification; that we have reviewed and understand the contents of the Specification indicated above, including the claims; that we do not know and do not believe that this design was ever known or used in the United States of America before our invention thereof, or patented or described in any printed publication in any country before our invention thereof, or in public use or on sale in the United States of America more than one year prior to this application; that this design has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by us or our legal representatives or assigned more than twelve months before this application; that we acknowledge our duties to disclose information of which we are aware which is material to the examination of this application under 37 C.F.R. §1.56(a), and that no application for patent nor inventor's certificate on this invention has been filed by us or our legal representatives or assigns in any country foreign to the United States of America.

As the named inventor, we hereby appoint Robert R. Deleault, Esq., Registration Number 39,165 as our attorney with full power of substitution and revocation to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

Robert R. Deleault, Esq.
Mesmer & Deleault, PLLC
41 Brook Street
Manchester, NH 03104
Tel: (603) 668-1971

We hereby declare further that all statements made herein of our own knowledge are true and that all statements made on information or belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

We hereby subscribe our names to the foregoing specifications, claims, declaration and power of attorney.

11-02-00 Date	Herbert M. Dean
Nov 2, 2000 Date	Robert E. Weinstein
11-08-00 Date	Allan M. Weinstein